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Effects of dopamine and bromocriptine on colonic motility in dog

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1 The effects of intravenous infusions of dopamine (0.1 to 1 mg $kg^{-1} h^{-1}$) and bromocriptine (10 to 40 $\mu g\, kg^{-1} h^{-1}$) on colonic motility were investigated in fasted dogs fitted with permanent strain gauges on the ascending, transverse and descending colon.

2 Infused at rates of 0.5 and 1 mg $kg^{-1} h^{-1}$ during 1 h, dopamine immediately stimulated the motility of the descending colon; after a delay of 40 to 60 min this effect was balanced by an inhibition of the motility of the ascending and transverse colon. Bromocriptine infused intravenously at doses of 10 to 40 $\mu g\, kg^{-1} h^{-1}$ stimulated the motility of the whole colon but these effects were limited to the duration of the infusion (60 min).

3 Both propranolol (0.5 mg kg^{-1}) and tolazoline (2 mg kg^{-1}) failed to block the effects of dopamine and bromocriptine whereas phentolamine (0.1 mg kg^{-1}) and prazosin (0.2 mg kg^{-1}) partially reduced the inhibitory effects of dopamine on the proximal colon. Haloperidol at doses higher than 0.2 mg kg^{-1} and domperidone blocked the bromocriptine-induced stimulation of colonic motility which was unaffected by previous treatment with α- and β-adrenoceptor blocking agents.

4 These results suggest that in the dog, dopamine and bromocriptine stimulate colonic motility through specific dopamine receptors. However, they suggest that the inhibitory effects of dopamine on the proximal colon which are blocked by dopamine antagonists are also partially due to an effect on α_1-adrenoceptors.

Introduction

Increasing evidence favours the view that dopamine may be an important neurotransmitter (Goldberg, 1972) and it has been proposed that dopamine mediates gastric relaxation through specific receptors (Valenzuela, 1976; Van Nueten & Janssen, 1978); dopamine receptors have also been found in oesophageal smooth muscle (De Carle & Christensen, 1976) and in the sigmoid colon (Lanfranchi *et al.*, 1978).

Dopamine increases motility of the distal colon (Lanfranchi *et al.*, 1978) in man and dopamine antagonists have been successfully employed in the treatment of many psychosomatic disturbances, particularly in the 'spastic colon' syndrome, and nervous diarrhoea (Lechin *et al.*, 1977a,b). Recently it has been shown that these substances are able to modify the motility of the distal colon in humans but the effects depend on the pre-existing pattern of motility (Lechin & Van der Dijs, 1979).

As far as we know, no experiments have been performed to test the effects of dopamine on colonic motility in conscious animals. The purpose of this study was (i) to describe the effects of dopamine infusion on colonic motility in dogs, a species presenting a well-defined cyclic pattern of contraction (Templeton & Lawson, 1936; Fioramonti & Bueno, 1983); (ii) to compare these effects with those of a potent dopamine agonist, bromocriptine (Riddall & Leavens, 1978; Robertson, 1980); (iii) to examine the nature of their effects using α- and β-blockers and specific dopamine antagonists.

Methods

Animal preparation

Six adult mongrel dogs weighing between 15 and 25 kg were used in these experiments. Under halothane anaesthesia (Fluothane N.D.) three strain gauge transducers, constructed in our laboratory according to the method previously described by Pascaud *et al.* (1978), were sutured in the colon at 2, 8 and 25 cm from the ileo-colonic junction. Each trans-

ducer had its recording axis parallel to the transverse axis of the intestine to record contractions of the circular smooth muscle. The free ends of the strain gauge wires were brought subcutaneously to the back of the neck and a silastic catheter was inserted into the right jugular vein. The dogs were allowed to recover for 10–15 days after the surgery before the experiments were started.

Recordings

The experimental animals were placed in modified metabolic cages and the colonic mechanical activity arising from the three transducers was recorded continuously during each experimental period by connecting the strain gauges to a 4-channel Wheatstone bridge amplifier (VT 2100, Vishay, France) connected to a potentiometric recorder (RKA, Rikadenki, Japan) and a magnetic tape recorder (Analog 7, Philips, Holland).

Quantitative computerized analysis was performed from stored data using a microcomputer data processor (PDS M 6800 Motorola, France) according to a technique described previously (Latour & Bueno, 1980). During computer analysis, the numerical values were plotted as a function of time permitting the running of the A/D converter to be controlled and giving a compressed view of an 8–10 h recording.

The motility index (MI) given by the processing system corresponded to the measurements of the area between the baseline and the contractile curve, i.e. the product of the amplitude (Y) expressed in g and the time (X) in min; the developed printing programme indicated intermediate consecutive values every 5, 30 and 60 min. Calibration of each strain gauge was performed before implantation with the establishment of individual calibration curves (Latour & Bueno, 1980).

Experimental procedure

During the first series of experiments performed in 12 h-fasted dogs, dopamine chlorhydrate (Simes Ltd, England) or bromocriptine methane sulphonate (Sandoz, Switzerland) were infused intravenously for 1 h at one of the three following rates: 0.1, 0.5 and 1.0 mg $kg^{-1} h^{-1}$ for dopamine and 5, 10 and 40 $\mu g\, kg^{-1} h^{-1}$ for bromocriptine. The infusions were performed twice on each animal and at 2-day intervals.

In another series of experiments, performed only in 4 dogs, infusions of dopamine (1 mg $kg^{-1} h^{-1}$) or bromocriptine (40 $\mu g\, kg^{-1} h^{-1}$) were repeated twice on each animal 20 min after a previous administration of phentolamine (0.1 mg kg^{-1}), prazosin (0.2 mg kg^{-1}), tolazoline (2 mg kg^{-1}), propranolol (0.5 mg kg^{-1}), haloperidol (0.1, 0.2 and 0.4 mg kg^{-1}) or domperidone (0.2 mg kg^{-1}). In order to verify the absence of any blocking effects of haloperidol and domperidone at α_1- and α_2-receptors, these two drugs were administered 20 min before intravenous injection of phenylephrine (0.2 mg kg^{-1}) or clonidine (10 $\mu g\, kg^{-1}$). The effects were compared to those of phenylephrine or clonidine given alone.

The motility index expressed in g min^{-1} per 60 min was measured 1 h before (control) and 2 h after the beginning of dopamine or bromocriptine infusion. The values obtained during and after the infusion were compared to those observed during the control period using the paired *t* test.

Results

Effects of dopamine

The direct record of colonic contractile activity obtained from each of the three gauges showed typical series of contractions lasting 4.9 ± 0.7 and 12.1 ± 3.2 min (mean ± s.d. for 6 animals) at 2 and 25 cm from the ileo-colonic junction respectively, and an intermediate duration (9.7 ± 1.3 min) on the transverse colon. They correspond to rhythmic contractile waves associated with an increase in the baseline at a frequency of 4.8 ± 0.7 and 3.7 ± 0.5 per min respectively at 2 and 25 cm from ileo-colonic junction (Figure 1). Digitalized records obtained after processing data analysis indicated that in the 15 to 22 h fasted dog, these groups of contractions occurred on the proximal colon at 21.6 ± 6.7 min intervals and were in 58% of the cases propagated aborally at a velocity of 5.2 ± 1.6 cm min^{-1} (Figure 1). They corresponded to an hourly motility index varying from 6.2 ± 1.5 to 8.2 ± 2.2 g $min^{-1} h^{-1}$ from the ascending colon to the descending colon without hourly significant ($P < 0.05$) variations from 15 to 22 h after a meal.

During dopamine infusion (0.5 mg $kg^{-1} h^{-1}$) the cyclic occurrence of contractions on the proximal and transverse colon, the mean amplitude of the contractions (4.2 ± 2.5 g vs 4.8 ± 1.7 g) and the motility indexes (Figure 2) were not significantly ($P > 0.05$) modified. In contrast, the motility of the distal part of the colon was immediately modified (Figure 1). The mean amplitude of the contractions (2.1 ± 0.8 g) was significantly ($P < 0.01$) reduced compared to that observed during saline infusion or control period, i.e. the last hour before the infusion period. However, the frequency of the contractions was more than doubled and consequently the motility index of the distal colon was significantly ($P < 0.05$) increased compared to the control period (Figure 2).

During the post-infusion period, the motility of the ascending and transverse colon was progressively

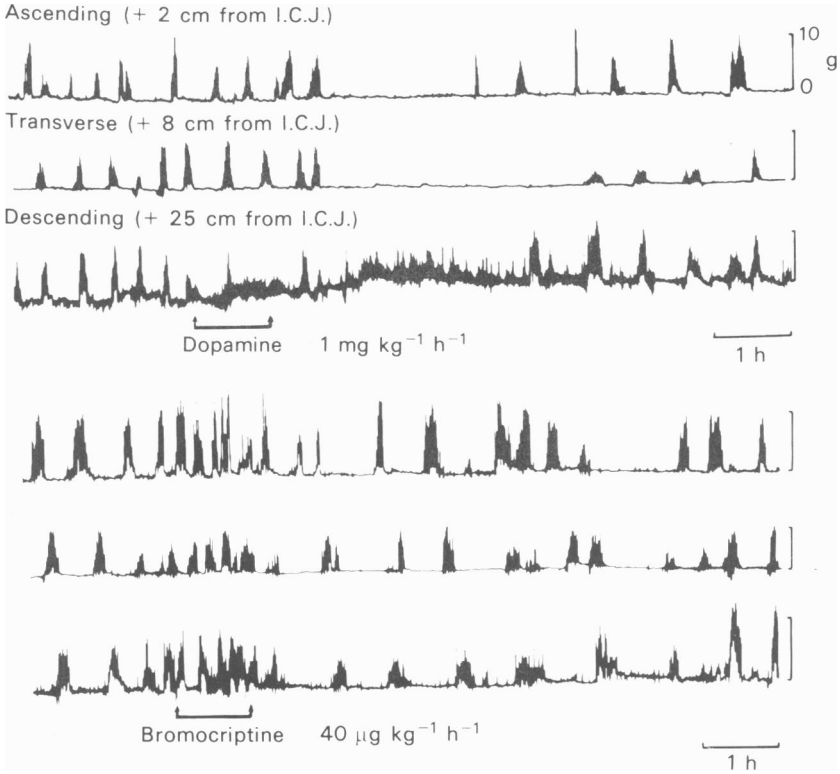

Figure 1 Comparative effects of dopamine and bromocriptine on colonic motility in the fasted dog. Dopamine infusion was followed by an inhibition of motility of the ascending and transverse colon associated with a stimulation of the distal colon. Bromocriptine induced a stimulation of all sites of the colon.

abolished for at least 90 to 100 min. The motility indexes measured from 60 to 120 min after the beginning of infusion were 24 and 36% of those observed for the ascending and transverse colon respectively during the 60-min control period. Concomitantly the dopamine-induced hyperactivity of the descending colon remained enhanced as judged by the significant increase (57.3%) in the motility index reaching 12.9 ± 1.5 g min^{-1} per h during the first post-infusion period vs 8.2 ± 2.2 g min^{-1} per h in the control period prior to infusion. The recovery of the cyclic pattern was first seen on the proximal part of the colon.

At the lowest infusion rate (0.1 mg kg^{-1} h^{-1}), disruption of the cyclicity of the motor pattern was limited to the descending colon and to the period of infusion. At the highest level (1 mg kg^{-1} h^{-1}), the inhibition of the colonic motility on the proximal part occurred less than one hour after the beginning of infusion with a shortened and less intense stimulatory effect on the distal colon (4 dogs). In 2 dogs, this dosage produced an inhibition of activity at each investigated site; consequently it was not possible to establish any dose-effect relationships.

Effect of bromocriptine

Infused at a rate of 10 μg kg^{-1} h^{-1}, bromocriptine stimulated colonic contractile activity, increasing the frequency of contractions and their phasic occurrence.

At the three dosages used, these stimulatory effects were observed at all the sites considered. The increase in the motility indexes was higher on the distal than on the proximal colon and at the highest dosage (40 μg kg^{-1} h^{-1}) these increases were respectively 60.6 and 33.2%, an intermediate increase being observed on the transverse colon (Figure 2).

These stimulatory effects of bromocriptine did not persist after the end of infusion and they were not followed by an inhibition of the colonic mechanical activity for the proximal and transverse portions as observed for dopamine (Figures 1 and 2). They were also similar in all the animals tested.

Effect of adrenoceptor antagonists

Intravenous administration of phentolamine (0.1

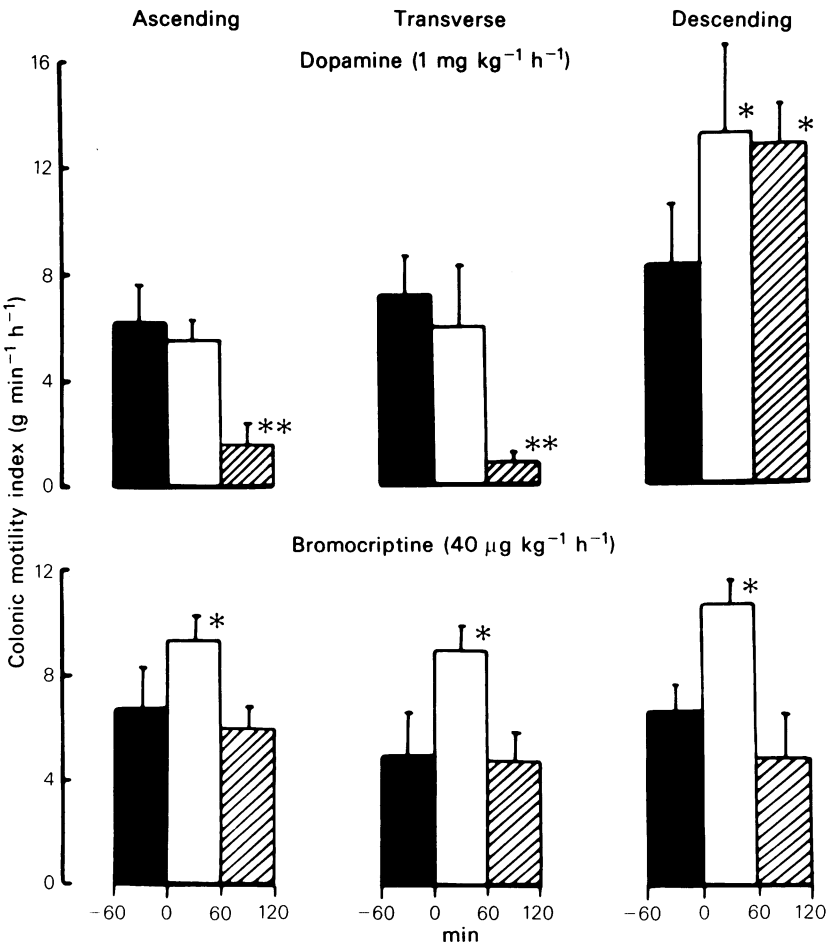

Figure 2 Effect of dopamine and bromocriptine infusions on the colonic motility indexes (MI) in 15–22 h fasted dogs. Mean for 2 trials in each of 4 dogs (dopamine) and 6 dogs (bromocriptine) is shown; vertical lines indicate s.e.mean. MI: see Methods for definition as determined for 60 min periods. $*P<0.05$; $**P<0.01$ compared with control values.

mg kg^{-1}), tolazoline (2 mg kg^{-1}), prazosin (0.2 mg kg^{-1}) or propranolol (0.5 mg kg^{-1}) did not affect significantly either the colonic motor profile or the motility index recorded at the three sites considered.

The hypomotility of the proximal and transverse colon induced by dopamine infusion (1 mg kg^{-1} h^{-1}) was reduced (Figure 3, Table 1) by previous administration of phentolamine (0.1 mg kg^{-1}) or prazosin (0.2 mg kg^{-1}). In contrast, this dopamine-induced inhibition was not modified by prior administration of tolazoline (2 mg kg^{-1}) or propranolol (0.5 mg kg^{-1}). None of the four adrenoceptor antagonists used modified the stimulation of the distal colon induced by dopamine infusion.

Similarly, the stimulatory effects of bromocriptine (40 μg kg^{-1} h^{-1}) on the ascending, transverse and descending colon were not affected by previous administration of phentolamine, tolazoline, prazosin or propranolol (Table 1).

Effects of dopamine antagonists

Haloperidol at doses of 0.1, 0.2 and 0.4 mg kg^{-1} or domperidone at a dose of 0.2 mg kg^{-1} given intravenously did not modify the colonic motor profile and the motility index at three levels investigated.

The two drugs did not modify the colonic response to the α_1- or α_2-adrenoceptor agonists, phenylephrine and clonidine. Intravenous injection of phenylephrine (0.2 mg kg^{-1}) induced a total inhibition of the motility at the three colonic sites during 47 ± 9 min. This inhibition was not modified by previous ad-

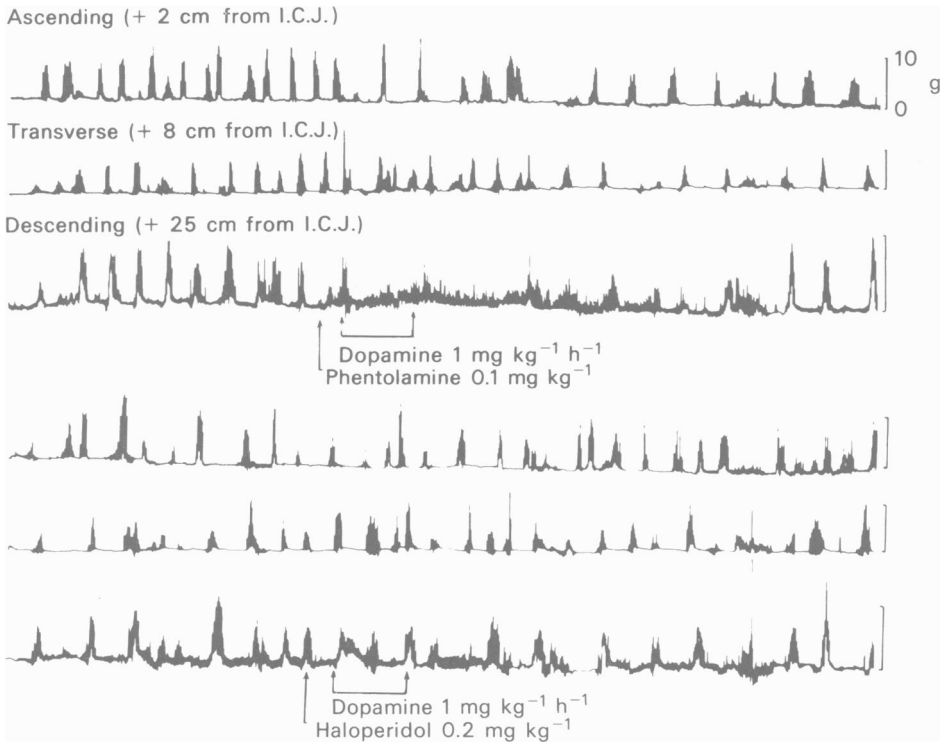

Figure 3 Comparative antagonism of phentolamine and haloperidol on dopamine-induced changes in colonic motility. Phentolamine reduced the dopamine-induced inhibition of the ascending and transverse colon but did not affect the stimulation of the distal colon. Haloperidol abolished all the effects of dopamine on proximal and distal colon.

Table 1 Comparative effects of phentolamine, tolazoline, prazosin and propranolol on dopamine- and bromocriptine-induced motor changes of the colon

	Dopamine post-infusion (+60/120)			*Bromocriptine* during infusion (0/+60)		
	Ascending	*Transverse*	*Descending*	*Ascending*	*Transverse*	*Descending*
Control[a]	1.6 ±0.8	0.9 ±0.5	12.9 ± 1.5	9.2 ± 0.9	8.9 ± 0.9	10.6 ± 0.8
Phentolamine 0.1 mg kg^{-1}	3.4* ±0.7	3.3* ±0.9	12.6 ± 4.1	10.1 ± 2.3	9.2 ± 1.8	10.8 ± 1.2
Tolazoline 2 mg kg^{-1}	1.2 ±0.9	1.5 ±0.8	13.8 ± 2.3	8.9 ± 0.9	10.4 ± 2.4	11.4 ± 2.9
Prazosin 0.2 mg kg^{-1}	3.9** ±1.2	2.1* ±0.8	13.6 ± 2.5	11.0 ± 1.2	7.8 ± 1.0	11.8 ± 1.4
Propranolol 0.5 mg kg^{-1}	0.9 ±0.7	1.6 ±0.9	11.4 ± 6.3	11.4 ± 3.4	10.5 ± 1.7	9.2 ± 0.6

Values are from 15–22 fasted dogs; mean ± s.d. for 2 trials in each of 4 dogs (dopamine) and 6 dogs (bromocriptine).
[a]Values observed from 60 to 120 min after the beginning of dopamine infusion (1 mg kg^{-1} h^{-1}) and during (0–60 min) that of bromocriptine (40 μg kg^{-1} h^{-1}).
Significantly different from control values at *$P < 0.05$ and **0.01.

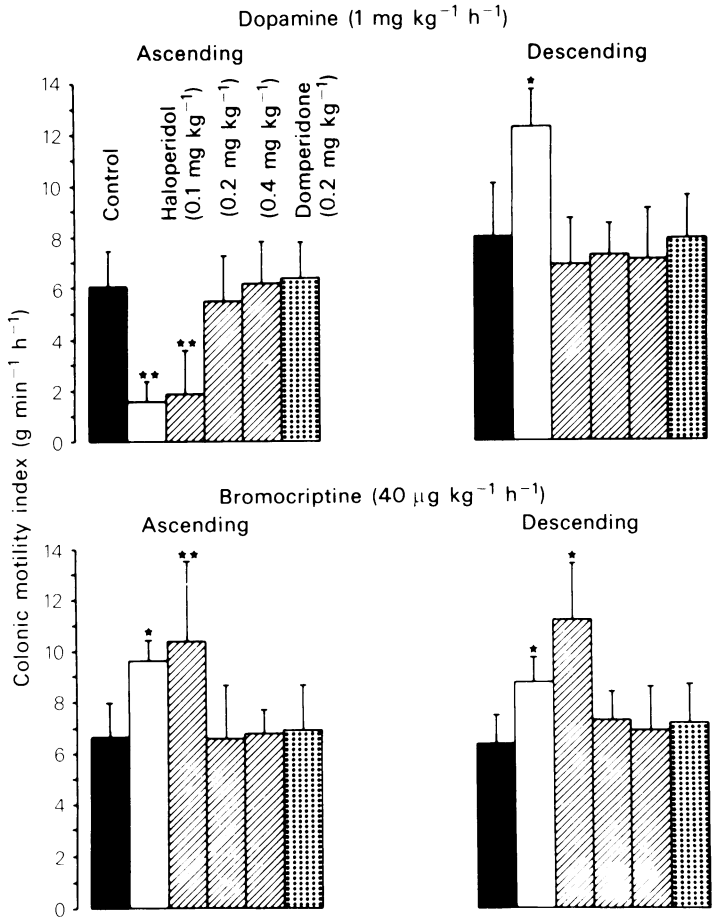

Figure 4 Influence of increased doses of haloperidol (0.1, 0.2, 0.4 mg kg^{-1}) and domperidone (0.2 mg kg^{-1}) on dopamine or bromocriptine (open columns) induced changes in the colonic motility indexes in 15–22 h fasted dogs. Motility indexes were determined 60 to 120 min after the end of dopamine infusion and during (60 min) the infusion of bromocriptine. Mean for 2 trials in each of 4 dogs; vertical lines show s.e.mean. $^{*}P < 0.05$; $^{**}P < 0.01$ compared with control values.

ministration of haloperidol (0.2 mg kg^{-1}) or domperidone (0.2 mg kg^{-1}). Similarly, colonic motility was inhibited during 98 ± 12 min after intravenous administration of clonidine. This response remained unchanged after haloperidol or domperidone.

At doses of 0.2 and 0.4 mg kg^{-1}, haloperidol abolished the motility changes induced by dopamine (1 mg kg^{-1} h^{-1}) on the proximal and distal colon. At a lower dosage (0.1 mg kg^{-1}), haloperidol blocked only the stimulatory effects of dopamine on the descending colon whereas the inhibition of the ascending and transverse colon persisted (Figure 4). The effects of dopamine at the three colonic sites were abolished by previous administration of domperidone (0.2 mg kg^{-1}).

At all dosages used haloperidol as well as domperidone blocked the stimulatory effects of bromocriptine (40 μg kg^{-1} h^{-1}) at the three colonic sites (Figure 4).

Discussion

The present study clearly establishes that dopamine and bromocriptine do not have the same effects on colonic motility except for the distal colon which is stimulated by these two substances.

The opposite effects produced by dopamine infusion on proximal and distal colon confirm the possibility of differential effects of drugs on these two

parts observed in man and supported by the presence of two neural control areas (Fink & Friedman, 1960). Abundant anatomical data have confirmed that in man as in dogs the vagus supplies parasympathetic preglanglionic fibres to the proximal half of the colon and that the nerve fibres arising from the second and third sacral nerves are distributed to the descending colon and rectum (Lannon & Weller, 1946).

Adrenoceptor agonists usually exert an inhibitory effect on colonic motility observed *in vitro* as well as *in vivo* by acting essentially on postsynaptic receptors (Burks, 1981). At the dosages used, dopamine has similar properties to adrenoceptor agonists on the proximal colon, inhibiting its motility. However, the present work indicates that these effects are partially due to an α_1-adrenoceptor-stimulation since prazosin and not tolazoline reduced the dopamine-induced inhibition. A dopamine component seems also to be involved in this inhibition since haloperidol, which did not block the effects of α_1- or α_2-agonists such as phenylephrine or clonidine on colonic motility, antagonized the response to dopamine.

Our results are in agreement with the stimulatory effect of dopamine on the distal colon described in man (Lanfranchi *et al.*, 1978) as well as the fact that α- and β-antagonists are not able to block these effects. Among the different sites of the gastro-intestinal tract investigated, gastro-oesophageal junction (Cox & Ennis, 1980), stomach (Sahyoun *et al.*, 1982), ileum (György *et al.*, 1981), only the distal colon seems to react to dopamine through specific dopamine receptors. The blockade of the dopamine-induced stimulation of the distal colon by haloperidol and domperidone, which does not cross the blood brain barrier, is in agreement with a specific dopaminergic action.

The uniform effects of bromocriptine on the whole colon and their blockade by both haloperidol and domperidone are in agreement with the presence of only specific excitation-mediating dopamine receptors in the colon of the dog. However, the presence of differential effects of dopamine and their partial antagonism with different blockers suppose a more complex motor control of colonic motility.

Consequently one may speculate that dopamine preferentially acts on inhibitory receptors of the proximal colon at the dosage used whereas bromocriptine – and perhaps dopamine at higher dosages – act preferentially on excitatory receptors. This hypothesis is in agreement with the relative potency of these substances previously observed on *in vitro* preparations, bromocriptine being 100 times (ponderal ratio) more active than dopamine (György *et al.*, 1981).

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References

BURKS, T. (1981). Action of drugs on gastro-intestinal motility. In *Physiology of the Gastro-intestinal Tract.* ed. Johnson, L.R. pp. 495–516. New York: Raven Press.

CARLE, D.J. DE & CHRISTENSEN, J. (1976). A dopamine receptor in oesophageal smooth muscle of the opossum. *Gastroenterology*, **70,** 216–219.

COX, B. & ENNIS, E. (1980). Mechanism of action of dopamine on the guinea-pig gastro-oesophageal junction *in vitro*. *Br. J. Pharmac.*, **71,** 177–184.

FINK, S. & FRIEDMAN, G. (1960). The differential effect of drugs on the proximal and distal colon. *Am. J. Med.*, **28,** 534–540.

FIORAMONTI, J. & BUENO, L. Diurnal changes in colonic motor profile in conscious dogs. *Dig. Dis. Sci.*, **28,** 257–264.

GOLDBERG, L.I. (1972). Cardiovascular and renal actions of dopamine: potential clinical applications. *Pharmac. Rev.*, **24,** 1–13.

GYÖRGY, L., ORR, Z. & DODA, M. (1981). Influence of dopamine and dopaminergic agonists on relaxation of isolated rabbit ileum induced by sympathetic nerve stimulation. *Acta Physiol. Acad. Sci. Hung.*, **58,** 163–168.

LANFRANCHI, G.A., MARZIO, L., CORTINI, C. & MORENO-OSSET, E. (1978). Motor effect of dopamine on human sigmoid colon. Evidence for specific receptors. *Am. J. Dig. Dis.*, **23,** 257–263.

LANNON, G. & WELLER, E. (1946). The parasympathetic supply of the distal colon. *Br. J. Surg.*, **34,** 373–376.

LATOUR, A. & BUENO, L. (1980). A micro-computerized system to measure the colonic contractile activity. *Int. J. Bio-Med. Comput.*, **11,** 389–396.

LECHIN, F., VAN DER DIJS, B., BENTOLILA, A. & PENA, F. (1977a). The 'spastic colon' syndrome: therapeutic and pathophysiologic considerations. *J. clin. Pharmac.*, **17,** 431–439.

LECHIN, F., VAN DER DIJS, B., BENTOLILA, A. & PENA, F. (1977b). Antidiarrheal effects of dihydroergotamine. *J. clin. Pharmac.*, **17,** 339–343.

LECHIN, F. & VAN DER DIJS, B. (1979). Effect of dopaminergic blocking agents on distal colon motility. *J. clin. Pharmac.*, **19,** 617–625.

NUETEN, J.M. VAN & JANSSEN, P.A. (1978). Is dopamine an endogenous inhibitor of gastric emptying? In *Gastrointestinal Motility in Health and Disease.* ed. Duthie, pp. 173–184. Lancaster: MTP Press.

PASCAUD, X.B., GENTON, M.J. & BASS, P. (1978). A miniature transducer for recording intestinal motility in unrestrained chronic rats. *Am. J. Physiol.*, **235,** E532–E538.

RIDDALL, L.R. & LEAVENS, W.J. (1978). Affinities of drugs

for the agonist and antagonists states of the dopamine receptor. *Eur. J. Pharmac.*, **51,** 187–188.

ROBERTSON, H.A. (1980). Stimulation of ^{3}H-apomorphine binding by dopamine and bromocriptine. *Eur. J. Pharmac.*, **61,** 209–211.

SAHYOUN, H.A., COSTALL, B. & NAYLOR, R.J. (1982). Catecholamines act at α_2-adrenoreceptors to cause contraction of circular smooth muscle of guinea-pig stomach. *J. Pharm. Pharmac.*, **34,** 381–385.

TEMPLETON, R.D. & LAWSON, H. (1936). Studies on the motor activity of the large intestine. *Am. J. Physiol.*, **96,** 667–676.

VALENZUELA, J.E. (1976). Dopamine as a possible neurotransmitter in gastric relaxation. *Gastroenterology*, **7,** 1019–1022.

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